

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21045

CORRESPONDENCE



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

April 27, 1999

VIA FACSIMILE AND FIRST CLASS MAIL

David G. Adams, Esq.
Venable, Baetjer, Howard & Civiletti, LLP
1201 New York Avenue, N.W., Suite 1000
Washington, D.C. 20005-3917

Re: Appeal of Decision of CDER's Labeling and Nomenclature Committee (NDA 21-045)

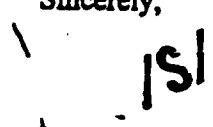
Dear Mr. Adams:

This is in response to your letter of March 28, 1999, appealing a decision on the trade name of an emergency contraception product, levonorgestrel, NDA 21-045.

I have reviewed this appeal, and find that the proposed trade name, "Plan B", is acceptable. Therefore your client, Women's Capital Corporation, may plan to use this name.

The fact that I find the name acceptable does not mean I agree with or accept the arguments you set forth in your March 29th letter.

Sincerely,


Janet Woodcock, MD.
Director,
Center for Drug Evaluation and Research

2-1
NDA 21-045

Women's Capital Corporation
Attention: Sharon Camp, M.D.
550 Kirkland Way
Suite 204
Kirkland, WA 98033

MAY 14 1999

Dear Dr. Camp:

Please refer to your pending January 29, 1999, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plan B (levonorgestrel) Tablets.

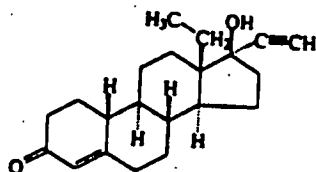
We also refer to your submissions dated April 12, 28 and 29, 1999.

We have completed our review of the Chemistry section of your submission and have the following comments and information requests:

1. Please provide the certificates of analysis (COA) for the gelatin used in the manufacture of tablets that did not fail dissolution testing when stored under accelerated conditions. The following are possible drug product batches from which the gelatin COA's can be provided: T73358, T73355, T69423 and 001.0394.
2. Please provide information on how long and under what conditions the bulk tablets are stored before blister-packaging. In addition, please provide information on the conditions of tablet blistering and the specifications for the in-process controls used during blistering.
3. Based on the drug product batch analysis results, the proposed specifications for Related Substances need to be revised as follows: total impurities %, 6-OH-levonorgestrel % and 10-OH-levonorgestrel %.
4. Please provide the temperature at which the dissolution test is performed.
5. A more legible copy of the validation report for the assay and related substances methods is needed.
6. In the "List of Samples to be Provided" section of the Methods Validation Package, the approximate quantity and lot number of each component to be provided to each FDA lab needs to be provided. In addition, once the Methods Validation Package is finalized, three complete copies need to be submitted.
7. Due to dissolution failures in all batches after two months and failures in three batches after one month of storage under accelerated conditions, and the lack of substantial room temperature data (nine months for one batch), a 6-month expiration date is recommended at this time. The 6-month expiration date should be calculated from the manufacturing date of the drug product tablet.

8. The **DESCRIPTION** section of the package insert should be revised to the following:

"Emergency contraceptive pill (ECP). Each Plan B™ 100 mg tablet contains 0.75 mg of the active ingredient, levonorgestrel, d(-)-13-beta-ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one, a totally synthetic progestogen. The inactive ingredients present are colloidal silicon dioxide, potato starch, gelatin, magnesium stearate, talc, corn starch, and lactose monohydrate. Levonorgestrel has a molecular-weight of 312.46, and the following structural and molecular formula:"



9. In the **HOW SUPPLIED** section of the package insert the storage statement should be revised to:
- "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]". In addition, a Rx statement needs to be added.
10. Please provide a sample of the shipping label that will be used on the outside of the bulk container containing the two-count blister packs.
11. Please provide a mock-up of the to-be-marketed secondary packaging container.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Jennifer Mercier, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/s/

5/14/99

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products.
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Page 4

cc:

Archival NDA 21-045

HFD-580/Div. Files

HFD-580/J.Mercier

HFD-580/Rhee/Lin/Rarick/Mann

HFD-820/DNDC Division Director (only for CMC related issues)

DISTRICT OFFICE

Drafted by: JM/May 13, 1999

Initialed by: May 14, 1999/Rumble

final: May 14, 1999

filename:

INFORMATION REQUEST (IR)

Kish

FEB - 3 1999

Women's Capital Corporation
Attention: Sharon Camp, Ph.D.
President & CEO
550 Kirkland Way
Suite 204
Kirkland, WA 98033

Dear Dr. Camp:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: levonorgestrel 0.75 mg tablets
Therapeutic Classification: Priority (P)
Date of Application: January 29, 1999
Date of Receipt: January 29, 1999
Our Reference Number: 21-045

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 30, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 29, 1999.

Under 21 CFR 314.102(c) of the new drug regulations you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA please contact Ms. Christina Kish, at (301) 827-4260.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room, Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Page 2

If you have any questions, contact Christina Kish, Project Manager, at (301) 827-4260.

Sincerely,

151
4/3/11
Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Archival NDA 21-045

HFD-580/Div. Files

HFD-580/C.Kish/L.Rarick/M.Mann/S.Salughter/D.Davis/M.Rhee/A.Jordan/A.Parekh/L.Kammerman

DISTRICT OFFICE

HFD-580/CKish/2.2.99/n21045ak

ACKNOWLEDGEMENT (AC)

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27 July 1999

Lisa Rarick, M.D., Division Director
Division of Reproductive and Urologic Health Products (HFD-580)
Center for the Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Serial No. 026
Final Package Insert

Dear Dr. Rarick:

Jennifer Mercier requested today two additional editorial changes to the final package insert submitted in Serial No. 025 on Friday July 23, 1999. This revised final version is enclosed.

Please do not hesitate to contact me with any comments or questions.

Cordially yours,

Sharon Camp
Sharon L. Camp, Ph.D.
President

Enclosures

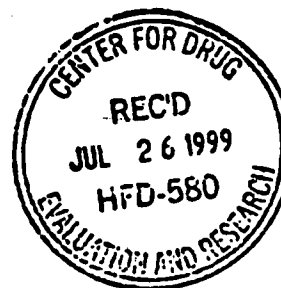
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WOMEN'S
CAPITAL
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23 July 1999

Lisa Rarick, M.D., Division Director
Division of Reproductive and Urologic Health Products (HFD-580)
Center for the Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Serial No. 025
Final Package Insert and Secondary
Packaging

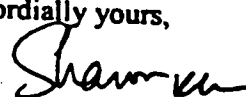
Dear Dr. Rarick:

Enclosed please find a copy of the final package insert text for Plan B™ (levonorgestrel) tablets, 0.75 mg, and of the user information to be printed on the secondary packaging (the four-fold card). Women's Capital Corporation (WCC) has modified these documents to include the editorial changes that Dr. David Lin requested last week.

The package insert is provided in Attachment 1. Secondary packaging for Plan B™ consists of two types of containers. The packet holds a two-count blister card, and the shelf-box (dispenser/packer) holds approximately 10 packets. FDA has approved user information to be printed on the secondary packaging holding the two-tablet blister card. This labeling is provided in Attachment 2. The labeling of the packet and shelf box have been changed so that they are consistent with the labeling provided in the package insert. A copy of the shelf box carton label text is provided in Attachment 3.

Please do not hesitate to contact me with any comments or questions.

Cordially yours,


Sharon L. Camp, Ph.D.
President

Enclosures

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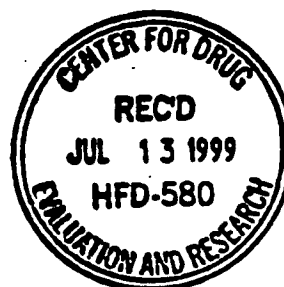


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12 July 1999



Lisa Rarick, M.D., Division Director
Division of Reproductive and Urologic Health Products (HFD-580)
Center for the Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Serial No. 023
Final Package Insert and Carton
Text

Dear Dr. Rarick:

Enclosed please find a copy of the final package insert text and the final proposed carton text. These have been provided as Attachment 1 and Attachment 2, respectively. Women's Capital Corporation (WCC) has modified these documents per the teleconference with the Division on July 9, 1999.

In addition, please find enclosed a copy of Women's Capital Corporation's Meeting Minutes from the teleconference with the Division on July 9, 1999 (Attachment 3). These minutes include the discussion of both labeling issues (package insert and carton text) as well as of chemistry, manufacturing and control issues.

Please be advised that WCC intends, prior to FDA action on the NDA, to change it's headquarters address to a post office box in the Seattle area. We will send you an address change as soon as it is final.

Please do not hesitate to contact me with any comments or questions.

Cordially yours,

Sharon Camp
Sharon L. Camp, Ph.D.
President

WOMEN'S
CAPITAL
CORPORATION



ORIGINAL

NEW CORRESP

NC

8 July 1999

Lisa Rarick, M.D., Division Director
Division of Reproductive and Urologic Health Products (HFD-580)
Center for the Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-045

Levonorgestrel Tablets
as Emergency Contraception
Core Launch Materials

Dear Dr. Rarick:

Please find enclosed core launch materials for Women's Capital Corporation's Plan B™ (levonorgestrel 0.75 mg tablet). We have provided one copy of this submission for your information. Two additional copies have been sent to Lisa Stockbridge, Ph.D., Division of Drug Marketing, Advertising, and Communications. The materials we have provided are listed below.

- Resource Kit for Health Care Providers which includes the following:

Manual for Health Care Providers

English Version of the Client Brochure

Fact Sheet for Plan B™

The Contraception Report Publication: Grimes, 1999

Lancet Publication: Task Force on Postovulatory Methods of Fertility
Regulation, 1998 and Guillebaud, 1998 editorial- to be
included as a single reprint

- Copies of Articles Referenced in the Manual for Health Care Providers
- Copy of the Final Proposed Package Insert for Plan B™

We understand from Jennifer Mercier, Project Manager, that the Division is presently reviewing the package insert and may have additional changes. Also, we have faxed to Jennifer Mercier some editorial changes to the carton text (text for user information on

Dr. Lisa Rarick
8 July 1999
Page 2

the packaging) and may have a few additional changes to propose in the next several days.

We look forward to receiving your comments. We plan on submitting additional launch materials (to include a poster, wallet card, and press kit) shortly. In addition, please be advised that our address has changed. We have moved our Washington, DC office to Welcome, Maryland. The new address can be found below. Please note that the telephone and fax numbers have remained unchanged.

Women's Capital Corporation
P.O. Box 370
Welcome, MD 20693
(P) 301-753-1926 (F) 301-753-1927

Cordially yours,

Sharon L. Camp

Sharon L. Camp, Ph.D.
President

Enclosures

cc: Lisa Stockbridge, Ph.D.
Division of Drug Marketing, Advertising, and Communications (HFD-40)

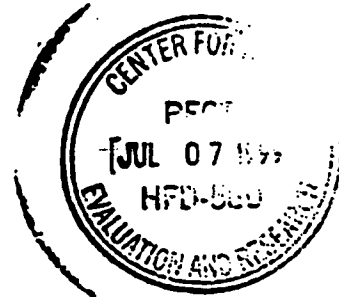
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6 July 1999

Lisa Rarick, M.D., Division Director
Division of Reproductive and Urologic Health Products (HFD-580)
Center for the Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Serial No. 022
Chemistry Amendment

Dear Dr. Rarick:

Please find herein additional Chemistry, Manufacturing and Controls (CMC) data. Specifically, the submission contains updated stability data, responses to Dr. Moo-Jhong Rhee's outstanding questions and comments (outlined in a letter dated 14 May 1999), and commitments requested in a telephone conversation with Dr. David Lin (date of telephone conversation 23 June 1999). As discussed in previous telephone conversations, these data are being submitted in time for review. The contents of this submission are further described below.

Women's Capital Corporation (WCC) has previously informed the Division that updated stability data will be provided in order to allow Dr. Rhee to agree to a longer expiration dating period than that proposed in his letter of 14 May (see Comment No. 7). Updated stability data for two-tablet blister packages of levonorgestrel 0.75 mg tablets, received from [redacted] and included in this submission, extend the amount of room temperature and intermediate temperature stability data available for one lot to 11 months and to 8 months the data for three additional lots of drug product. These commercial scale batches of drug product are actually 17 months and 12 months old, respectively, owing to the gaps between the date of manufacture and the start of stability studies on two-tablet blister packages. As outlined in the Discussion Paper provided in Attachment 1, the tablets on stability test show no downward trend in dissolution values when stored at long-term and intermediate stability conditions. WCC believes that the projections of available dissolution, assay, and impurities values out to 24 months indicate that the tablets would remain within all release specifications well beyond the 15-month proposed expiration dating period.

1290

Dr. Lisa Rarick
6 July 1999
Page 2

WCC's summary of the stability data available to-date and the updated stability report from [redacted] are supplied in Attachment 1. As requested by the FDA Chemistry Reviewer, Dr. Lin, WCC formally acknowledges by this submission that the expiration dating period starts at the date of manufacture.

This submission also contains responses to Dr. Rhee's other outstanding questions and comments. For reviewer convenience, a copy of Dr. Rhee's 14 May letter and all responses, including those previously made, are compiled in Attachment 2.

[redacted] has informed WCC in writing that bulk tablets are always stored at controlled room temperature conditions prior to packaging. [redacted] reports that monitoring data from the storage area show variations in temperature of 18 to 23°C and variations in relative humidity values of 50 to 70%. It is WCC's understanding that bulk tablets will be stored at [redacted] at controlled conditions meeting FDA requirements. It is WCC's intention to package the 1 million tablets remaining from the 18 May 1999 batch that are currently stored at [redacted].

The final Methods Validation Package is included in this submission and includes those elements requested by Dr. Rhee (see Comment No. 6 of the 14 May letter. The revised Methods Validation Package has been included as the last attachment of this submission (Attachment 3). As requested, three additional copies of this attachment are being provided with this submission.

In summary, this is the final CMC submission planned by WCC. With this submission, WCC has responded to all of Dr. Rhee's requests as fully as possible and complied with Dr. Lin's telephone requests. Please contact me if you have any more questions concerning this information.

Cordially yours,

Sharon L. Camp

Sharon L. Camp, Ph.D.
President

Desk Copy: Moo-Jhong Rhee, Ph.D.

Enclosures (including three desk copies of the Methods Validation Package)

WOMEN'S
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ORIGINAL
ORIGINAL AMENDMENT

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28 June, 1999

Lisa Rarik, M.D., Director
Division of Reproductive and Urologic Health Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857



Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Serial No. 021
Final Proposed Labeling

Dear Dr. Rarik:

On June 14, 1999, Women's Capital Corporation (WCC) received a facsimile of the final wording for Plan BTM emergency contraception label from Jennifer Mercier, Project Manager. Enclosed please find a copy of the final version of the proposed label. This label incorporates all FDA and WCC revisions to date, as well as the two modifications WCC noted in Serial No. 020, submitted to the FDA on 21 June, 1999.

Please note an additional two changes that have been made to the final proposed version of the label.

- Under the Contraindications Section, Ectopic Pregnancy subsection, the second sentence in this paragraph has been changed to read "Up to 10% of pregnancies reported in clinical studies of routine use of progestin-only contraceptives are ectopic." This sentence has been changed to reflect current grammatical usage.
- Under the Dosage and Administration Section, second paragraph, the word "patient" has been changed to "user".

Please do not hesitate to contact me with any additional comments.

Cordially yours,

Sharon Camp
Sharon L. Camp, Ph.D.
President

Enclosures

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21 June, 1999

Lisa Rarik, M.D., Director
Division of Reproductive and Urologic Health Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857



Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Serial No. 020
Proposed Information for
Users

Dear Dr. Rarik:

On June 11, 1999, Women's Capital Corporation (WCC) completed discussions with the Division on the final wording of the label for PLAN B emergency contraception.

Enclosed please find a draft of proposed "Information for the User" to be included at the bottom of the label. WCC also intends that this exact language will be printed on the 8 panels of the secondary packaging (a four-fold double-layer card into which the blister-packaged tablets are sealed). The proposed layout is also enclosed. It is WCC's strong belief that safe, effective and appropriate use of PLAN B can best be assured if important user information cannot become separated from the tablets. We have made every effort to keep the packaging and instructions simple and reassuring for the user who may be under considerable stress following unprotected intercourse.

The proposed Information for the User has been tested for reading comprehension by our colleagues at the Program for Appropriate Technology in Health. The reading level is grade 7.6. We have also conducted a study of the packaging, including the revised text, with potential prescribers. Please let me know if Division staff would like a copy of the study.

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In reviewing the new version of the primary label, faxed to us by Jennifer Mercier on June 14, 1999, we noted two small items:

1. Line 11: The d should be italicized, as in [*d*(-)-13 beta-ethyl-17-alpha-ethinyl-17 etc.].
2. Line 15: the word formula should be plural.

WCC will make these corrections and will add the chemistry formulation back into the text below the diagram.

Thank you for your cooperation in moving quickly to resolve the outstanding labeling issues. We look forward to having your comments on the proposed User Information at your earliest convenience. Final agreement on this language will allow us to finalize our packaging on schedule. This will, in turn, increase the chance that WCC will be in a position to ship drug product soon after we receive FDA approval.

We expect to provide the additional stability data Dr. Lin agreed to review, along with a proposal for expiration dating, in the week following the July 4 holiday.

Cordially yours,

Sharon Camp

Sharon L. Camp, Ph.D.
President

Enclosures

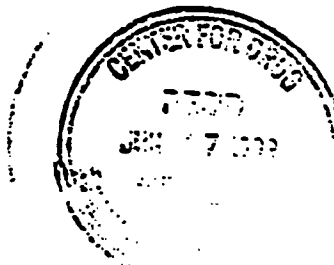


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June 17, 1999

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader,
Division of Reproductive and Urologic Drug Products
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Re: NDA 21-045
Levonorgestrel Tablets as
Emergency Contraception
Serial No. 019
Response to Questions (CMC)

Dear Dr. Rhee:

Please find below responses to comments and requests relative to your review of the Chemistry, Manufacturing, and Controls (CMC) section of our New Drug Application (NDA) for levonorgestrel (PLAN B™) tablets. These comments and requests were provided in your letter of May 14, 1999. Please reference my letter of May 18, 1999 in which we responded to items 5, 8, 9, and 11 of your letter. We had also asked to respond in writing to the comments and information requests in items 1, 2, 3, 4 and 10 of your letter. Each question is re-stated verbatim below in bold, followed by responses.

1. Please provide the certificates of analysis (COA) for the gelatin used in the manufacture of tablets that did not fail dissolution testing when stored under accelerated conditions. The following are possible drug product batches from which the gelatin COAs can be provided: T73358, T73355, T69423, and 001.0394.

COAs for three lots of gelatin supplied by are provided in Attachment 1. Lot PL-T228-96 was used to manufacture levonorgestrel 0.75 mg tablet lot T69423. Lot PL-U306-96 was used in drug product Lots T73355 and T73358, and gelatin Lot PL-M304-93 was used in the manufacture of drug product Lot 001.0394. Because of the poor quality of the COA for Lot PL-T228-96, a re-typed version is also provided.

2. Please provide information on how long and under what conditions the bulk tablets are stored before blister-packaging. In addition, please provide information on the conditions of tablet blistering and the specifications for the in-process controls used during blistering.

Bulk tablets are stored in the plant at 15 to 30°C and <70% relative humidity before blister packaging. Bulk tablets are generally packaged within a week of manufacture. Occasionally, tablets have been stored for several months prior to packaging, and tablets can be stored up to one year before packaging. has conducted stability studies on bulk tablets stored for 12 months at 25°C/60 %RH and for 9 months at 40°C/75 %RH. (The stability tests were conducted using tablets manufactured prior to 1998.)

With respect to tablet blister packaging, blister closing tests (i.e., leak test) are performed every hour using a LIPPKE VC 1350 package testing instrument. Filling control is monitored electronically by the filling machine Specifications for all in-process testing will be provided as soon as they are received from

3. Based on the drug product batch analysis results, the proposed specifications for Related Substances need to be revised as follows: total impurities %, 6-OH-levonorgestrel %, and 10-OH-levonorgestrel %.

will change the specifications for Related Substances in the drug product to: total impurities %, 6-hydroxy-levonorgestrel %, and 10-hydroxy-levonorgestrel %.

4. Please provide the temperature at which the dissolution test is performed.

Dissolution tests are performed at according to the USP requirements (i.e., 37°C ± 0.5°C).

10. Please provide a sample of the shipping label that will be used on the outside of the bulk container containing two-count blister packs.

A copy of the shipping label is provided in Attachment 2.

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

Dr. M.J. Rhee
June 17, 1999
Page 3

has not yet provided us with a "list of samples to be provided" (Item 6 of your letter). We will forward that information as soon as it is available. Also, as mentioned in my letter of May 18, 1999, we will be responding at a later time to FDA's current recommendation on an expiration dating period (Item 7 of your letter).

Very sincerely yours,

Sharon Camp (rs)

Sharon L. Camp, Ph.D.

ORIGINAL

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10 June 1999

Lisa Rarick, M.D.

Director

Division of Reproductive and Urologic Drug Products

Food and Drug Administration

Parklawn Building, Room 17-B45

5600 Fishers Lane

Rockville, Maryland 20857

Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Serial No. 018
Proposed Draft Labeling (Revision No .2)

Dear Dr. Rarick:

Please refer to your facsimile dated June 7, 1999 with recommendations for the draft label for levonorgestrel as emergency contraception. Women's Capital Corporation (WCC) has reviewed this version, and agrees with the majority of the changes. We assume that the Description section and the table of pharmacokinetic parameter values have now been reviewed by the appropriate disciplines. The revised draft label (Revision No. 2) is provided in Attachment 1. A version that contains the highlighted changes relative to the FDA recommended version can be found in Attachment 2. Finally, for your convenience, a copy of the FDA proposed text is included in Attachment 3.

In the balance of this letter, all changes in Revision No. 2 that differ from FDA recommendation are identified, with reference to the line numbers of the new proposed text and the FDA text. When appropriate, an explanation is included.

1. Line 3 of Revision No. 2: Addition of "Rx Only". This text has been moved from its original placement at the end of the label (Line 257 of FDA version dated June 7, 1999).
2. Line 7 of Revision No. 2 (Line 6 of FDA version): Typographical error in the word "ethinyl" has been corrected.
3. Line 68 of Revision No. 2 (Line 66 of FDA version): Deletion of the "s" in Indication.

1227

Dr. Rarick,
10 June 1999
Page 2

4. Line 71 of Revision No. 2 (Line 69 of FDA version): Addition of the word "first", to read "the first tablet should be taken as soon as possible within 72 hours of intercourse".
5. Section titled "Clinical Studies" beginning on Line 81 of Revision No. 2 (Line 79 of FDA version): WCC has modified this section by the addition of a sentence that we believe describes results in a more understandable fashion. This is also consistent with the approach taken in the PrevenTM label.
6. On Lines 96 and 99 of Revision No. 2 (Lines 134 and 138 of FDA version), "one year" has been changed to "1 year" for consistency. Similarly, on line 109 of Revision No. 2 (Line 147 of FDA version), "six months" has been changed to "6 months".
7. Lines 99 to 101 of Revision No. 2 (Lines 138 and 139 of FDA version) have been modified in order to be consistent with the original Trussell article (Footnote 4). The numbers in the table are based on 89% and without the additional explanatory sentence, the footnote may appear to be in contradiction to the table.
8. Under Contraindications, Line 111 of Revision No. 2 (Line 156 of FDA version) the typographical error in "contraceptives" has been corrected.
9. In the section titled "Ectopic Pregnancy" beginning on Line 132 of Revision No. 2 (Line 177 of FDA version); WCC believes that "woman-years" is difficult to interpret and that describing the number of ectopic pregnancies in relation to the total number of pregnancies is more meaningful. Therefore, alternate language is proposed based on CDC reporting (the citation MMWR, January 27, 1995 / 44(03):46-48 will be added to the references). In addition, the sentence referring to incidence in clinical trials has been removed, as it was originally intended to introduce the WHO study results, and is no longer relevant.
10. On Line 159 of Revision No. 2 (Line 203 of FDA version), the trade mark symbol has been added to PLAN BTM.
11. Lines 248 and 249 of FDA version: With respect to the Dosage and Administration section, we propose not including the sentence that reads, "If vomiting occurs within 3-4 hours of either dose of PLAN B, repeat dosing and antinausia (*sic*) medications may be considered." While the protocol recommended that a third tablet be taken in the event of vomiting within the first 4 hours, few women did. As noted by FDA, 55 women vomited within 7 days of dosing (5.6%); however, only 40 of these women ingested a third tablet for this reason, either following the first dose (17 patients or 1.7%) or the second dose (23 patients or 2.4%). WCC does not believe that it is warranted to base dosage instructions on such few subjects, especially when there has

Dr. Rarick,
10 June 1999
Page 3

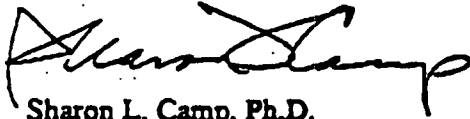
been no demonstrable effect on efficacy. Furthermore, unless drug is seen in the vomitus, there seems to be little pharmacologic rationale for this recommendation. Levonorgestrel is rapidly absorbed, with a mean time to peak concentration of 1.6 hours post-dose, and early vomiting may be considered evidence that the drug has in fact been absorbed. If FDA remains of the opinion that a third tablet should be recommended for women who vomit, WCC proposes to limit the recommendation to those women who vomit within the first 1 hour, consistent with the Preven™ labeling.

With respect to the recommendation to use anti-nausea medication, this instruction was not included in the dosing instructions in the clinical study. WCC is not aware of any data to support their use in this setting, however, is amenable to including this instruction.

12. In the How Supplied Section, WCC has added language to clarify that the product is supplied in units for a single course of treatment.

I will be pleased to speak with FDA officials late Friday afternoon, as proposed, should there be any outstanding issues at the end of your meeting.

Very cordially yours,



Sharon L. Camp, Ph.D.

Enclosures

WCC
PITAL
ORATION

ORIGINAL

ORIG AMENDMENT

BM

2 June 1999

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857



Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Serial No. 017
FDA Request for Information: Clinical

Dear Dr. Rarick:

In a recent telephone call during the week of May 3rd, 1999 with the Division, Women's Capital Corporation was asked to provide copies of Diary Cards from three randomly chosen subjects from each of the 21 sites of Study #92908. The subjects were identified by the Division. Enclosed please find copies of Diary Cards from 16 of the sites. The Diary Cards included in this package are listed in a table on the following page for your convenience. Please note that, as discussed with Jennifer Mercier on 15 May, 1999, if the requested Diary Card was not available, WCC has substituted another randomly chosen subject. These three cases where this was necessary are identified on the table.

Diary Cards are pending from five sites (9, 302, 1195, 1489, and 1757). These will be forwarded upon receipt from the study sites. If you have any questions, please do not hesitate to contact us.

Very cordially yours,

Sharon Camp
Sharon Camp, Ph.D.

Enclosure

cc: D. Davis, M.D., Medical Reviewer

6/3 Review pending
Nari

REVIEWS COMPLETED		
CSO ACTION:		
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CSO INITIALS <i>jm</i>		DATE <i>6/3/99</i>

1175

550 Kirkland Way, Suite 204, Kirkland, WA 98033, Tel. 425-739-2006, Fax 425-739-2036, Internet: seattle@thewcc.com

WOMEN'S
CAPITAL
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ORIGINAL

NEW CORRESP

NC

AS 6/1/99

26 May 1999

Lisa Rarick, M.D.

Director

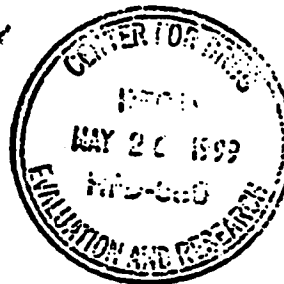
Division of Reproductive and Urologic Drug Products

Food and Drug Administration

Parklawn Building, Room 17-B45

5600 Fishers Lane

Rockville, Maryland 20857



noted
DTC
6/1/99

Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Serial No. 016
CMC Meeting Minutes

Dear Dr. Rarick:

Enclosed please find a copy of Women's Capital Corporation's Meeting Minutes from the CMC meeting on April 26, 1999. We are still working with consultants on the stability issue and will have additional information for you shortly. If you have any questions, please do not hesitate to contact us.

Very cordially yours,

Sharon Camp

Sharon L. Camp, Ph.D.

Enclosure

NAI - Dano - 5/28

REVIEWS COMPLETED	
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<input type="checkbox"/> MEMO	
CSO INITIALS	DATE

6/2/99

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WOMEN'S
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DUPLICATE

ORIG AMENDMENT

B2

26 May 1999

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857



Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Serial No. 015
Proposed Draft Labeling (Revised)

Dear Dr. Rarick:

Please refer to your facsimile dated May 20, 1999 with recommendations for the draft label for levonorgestrel as emergency contraception. Women's Capital Corporation (WCC) has reviewed the label, and includes herein a revised draft. Since our comments are numerous, they are provided as a separate attachment to this letter (Attachment 1) and are organized by section. The revised draft label is provided in Attachment 2, including one version that is line-numbered. This is intended to facilitate future communications about additional changes. Finally, for your convenience, a copy of the FDA proposed text is included in Attachment 3.

If you have any questions, please do not hesitate to contact me.

Very cordially yours,

Sharon L. Camp

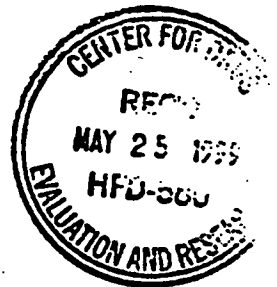
Sharon L. Camp, Ph.D.

Enclosures

WOMEN'S
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ORIGINAL
ORIG AMENDMENT
N-BM

May 25, 1999



Lisa Rarick, M.D.
Division Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Serial No. 014
FDA Request for Information: Clinical

Dear Dr. Rarick:

In a recent telephone call on the 19th of May, 1999 with Jennifer Mercier, Project Manager, WCC was asked to provide a by-subject listing of pregnancy test availability that includes all women in Study #92908 and whether or not they had the following:

- A urinary pregnancy test at enrollment.
- A blood draw at enrollment for use in the event of pregnancy post-treatment.
- A serum pregnancy test performed from a blood sample drawn at the time of enrollment.
- A urinary test at the follow-up visit.
- A serum pregnancy test performed at the follow-up visit.

This listing is enclosed along with an electronic copy for your convenience. In the same telephone call, Ms. Mercier requested selected Case Report Forms and Diary Cards from each site. WHO is in the process of collecting the information and we anticipate receiving the documents in approximately one week. Please let me know if you need any other information.

Very cordially yours,

Sharon Camp
Sharon Camp, Ph.D.

President

cc: Dr. Davis, M.D., Medical Reviewer

5/28 - will review / I have a copy

REVIEWS COMPLETED		
CSO ACTION:		
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.	<input type="checkbox"/> MEMO
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WOMEN'S
CAPITAL
CORPORATION

ORIGINAL

ORIGINAL AMENDMENT

BC

May 21, 1999

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for the
Division of Reproductive and Urologic Drug Products
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20857



Re: NDA 21-045
Levonorgestrel Tablets as
Emergency Contraception
Serial No. 013
Response to FDA Request for Information

Dear Dr. Rhee:

Please refer to your letter of May 14, requesting certain documents from Women's Capital Corporation. You requested a more legible copy of the validation report for the assay and related substances HPLC methods, as well as a sample of the shipping label that will be used on the outside of the bulk container containing the two-count blister packs. These items are enclosed.

Also enclosed is the mock-up of the proposed commercial package (minus art work), showing how the two-count blister packs produced by [redacted] will be sealed between the two-layer, four-fold secondary packaging. The secondary packaging is being done by [redacted].

Please let us know if you require anything further.

Sincerely yours,


Sharon L. Camp, Ph.D.
President

OK - 5/27 - [Signature]
To Chemist

REVIEWS COMPLETED	
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DATE	DATE

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Validation of NDA
Partly Test

Active Substance Content

WOMEN'S
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CORPORATION



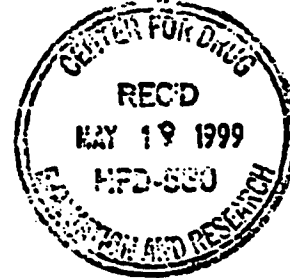
ORIGINAL

ORIG AMENDMENT

BC

May 18, 1999

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for the
Division of Reproductive and Urologic Drug Products
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20857



Re: NDA 21-045
Levonorgestrel Tablets as
Emergency Contraception
Serial No. 012

Dear Dr. Rhee:

Thank you for your letter of May 14, 1999. Please find below our response to the FDA's comments and requests relative to your review of the Chemistry, Manufacturing, and Controls (CMC) section of our New Drug Application (NDA) for levonorgestrel (PLAN B) tablets.

We have asked _____ to respond in writing to the comments and information requests in items 1 through 4. The request was faxed to _____ on Sunday, May 16, 1999. As you may recall, FDA field inspectors are visiting the plant on May 17 to 20, 1999. Therefore, the response from _____ may be delayed a few days.

Dr. Gordon Duncan is mailing me from our Seattle headquarters a legible copy of the validation report for the assay and related substances: _____ methods, as requested in item 5 of your letter. He is also sending a sample of the shipping label that will be used on the outside of the bulk container containing the two-count blister packs, as requested in item 10. These documents should arrive in a few days, and will be forwarded to you.

Women's Capital Corporation (WCC) will ensure that, in the "List of Samples to be Provided" section of the Methods Validation Package, the approximate quantity and lot number of each component to be provided to each FDA lab is listed. Three complete copies of the final Methods Validation Package will be provided to the FDA.

As requested in item 8, WCC will modify the DESCRIPTION section of its proposed package insert to conform to the text and diagram provided in your letter. However, we would like to

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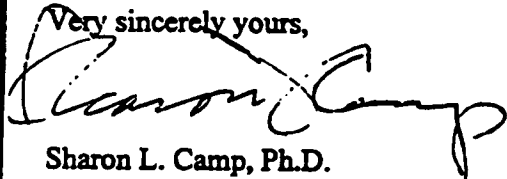
550 Kirkland Way . Suite 204 . Kirkland, WA 98033 . Tel. 425-739-2006 . Fax 425-739-2036 . Internet: seattle@thewcc.com

refer to the drug product as an "Emergency contraceptive tablet" and would prefer to drop the acronym (ECP). The acronym is familiar to a relatively limited number of U.S. health care providers and may be confused with an older acronym. WCC will also revise the HOW SUPPLIED section of the package insert, as recommended, with respect to storage conditions. An Rx only statement will be added to the package insert.

On May 1, 1999, we asked our secondary packager, to prepare new mock-ups of the secondary packaging container, showing how the blister packages will be permanently sealed between the two layers of card that form the four-fold package. These should be ready very soon. The text and art work, designed by our ad company in Seattle, will not be included on this new version. We assume that the mock-up included in the NDA will serve to illustrate the proposed text and art work.

We will be responding at a later time to the FDA's current recommendation on an expiration dating period. Because of the plant closings at it has been necessary to manufacture tablets this month in order to ensure that we will be able to supply the U.S. market at the time of approval. An expiration dating period of only 6 months will allow us to keep drug product on the market only two or three months at best. We are working with and with several consultants, on the stability issue and hope that the FDA will continue to keep the door open to all reasonable proposals.

Very sincerely yours,



Sharon L. Camp, Ph.D.

REVIEWS COMPLETED	
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reviewed
no CMC info
DTL
5/12/99



6 May 1999

Lisa Rarick, M.D.

Director

Division of Reproductive and Urologic Drug Products

Food and Drug Administration

Parklawn Building, Room 17-B45

5600 Fishers Lane

Rockville, Maryland 20857

AT 5/12/99

Re: NDA 21-045

Levonorgestrel Tablets

as Emergency Contraception

Serial No. 011

Response to FDA Request for Information

Dear Dr. Rarick:

Enclosed please find a copy of a package of information recently sent to Dr. Gurston D. Turner, Division of Scientific Investigations in the Office of Compliance. Dr. Turner requested this information for the upcoming inspections of the sites of the WHO/HRP Study 92908. The package includes:

- Copies of odd-numbered case report forms from the study site
- Copies of odd-numbered case report forms from the study site
- Adverse event listings for the study site
- Adverse event listings for the study site
- A copy of the study protocol
- A copy of the annotated case report form

Each of the above have been separated by tabs, for convenience. If you have any questions, please do not hesitate to contact us.

Very cordially yours,

Sharon L. Camp, Ph.D.
Sharon L. Camp, Ph. D. K84
President

Enclosure

REVIEWS COMPLETED	
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CSO INITIALS	DATE

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WOMEN'S
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ORIG AMENDMENT

April 28, 1999

Lisa Rarick, M.D.
Division Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857

BC
Reviewed.
See Chem Rev. #1
dated 5/12/99.
TC
5/13/99



Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
CMC Amendment
Serial No. 007

Dear Dr. Rarick:

Please find enclosed an amendment to the dissolution report submitted in CMC Amendment Serial Number 003 to NDA 21-045. The amendment to the dissolution report provides a replacement page for Page 0182 of the original report. A comment on systems suitability was inadvertently left off the original page. The replacement page contains the appropriate comment.

Please do not hesitate to call in the event of questions.

Very cordially yours,

Sharon Camp SMH

Sharon L. Camp, Ph.D.
President

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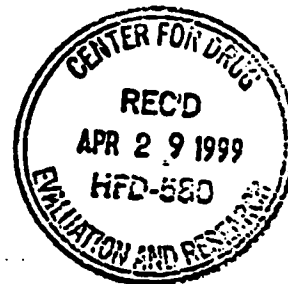
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Reviewed.
See *Chen*. Rev. #1
dat of 5/12/99.
DTC
5/15/99

April 29, 1999

Lisa Rarick, M.D.
Division Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857



Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Serial No. 010
CMC Amendment

Dear Dr. Rarick:

Please find enclosed updated stability data received from (Addendum
(2) to Postinor Tablets, Stability documentation, D-0129/4/St/3 US"). These data,
described in the attached document, are current through 28 April 1999. As indicated in
the summary table, 6-month data for three batches of two-tablet blister packages and
9-month data for one batch are now available. Results indicate that levonorgestrel
0.75 mg tablets manufactured after the September 1997 renovation remain within
specifications when stored at 25°C/60% RH and 30°C/60% RH for up to 9 months.

We trust that submission of these data, which had been anticipated for today, will not
result in a delay in the review time clock. Please let me know if I am in error on this
point.

Very cordially yours,

Sharon Camp SMH

Sharon Camp, Ph.D
President

irkland Way . Suite 204 . Kirkland, WA 98033 . Tel. 425-739-2006 . Fax 425-739-2036 . Internet: seattle@thewcc.com

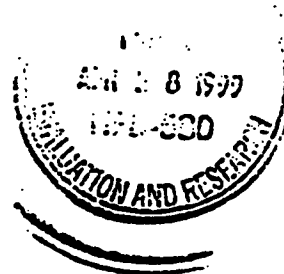
WOMEN'S
CAPITAL
CORPORATION



ORIGINATE
ORIG AMENDMENT
BM

28 April 1999

Lisa Rarick, M.D.
Division Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857



Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Serial No. 009
Response to FDA Request (Clinical)

Dear Dr. Rarick:

Please refer to WHO/HRP 1998 - Study 92908, the pivotal clinical study included in NDA 21-045. In response to a request made by Christina Kish on 14 April 1999, please find enclosed copies of diary cards for two centers. Diary cards for the site are provided in Attachment 1, and cards for the site are in Attachment 2.

Please do not hesitate to contact me in the event of further questions.

Very cordially yours,

Sharon Camp SMH

Sharon Camp, Ph.D.
President

550 Kirkland Way . Suite 204 . Kirkland, WA 98033 . Tel. 425-739-2006 . Fax 425-739-2036 . Internet: seattle@thewcc.com

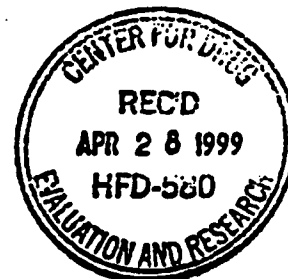
WOMEN'S
CAPITAL
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DUPLICATE
ORIGINAL AMENDMENT
SV

April 28, 1999

Lisa Rarick, M.D.
Division Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857



Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Safety Update
Serial No. 008

Dear Dr. Rarick:

Pursuant to 21 CFR 314.50, please find enclosed the Safety Update to NDA 21-045 for levonorgestrel 0.75 mg tablets for use as emergency contraception. This Safety Update provides an update of ongoing studies, newly published information, and post-marketing information. There are no new safety data that result in modification of the proposed labeling as submitted in the original New Drug Application.

Please do not hesitate to call in the event of questions.

Very cordially yours,

Sharon Camp SM

Sharon L. Camp, Ph.D.
President

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CAPITAL
CORPORATION

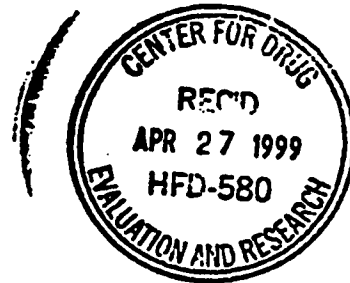


DUPLICATE

ORIG AMENDMENT

27 April 1999

Lisa Rarick, M.D.
Division Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857



Re: NDA 21-045
Levonorgestrel Tablets
As Emergency Contraception
Serial No. 006
Information Amendment (Clinical)

Dear Dr. Rarick:

At the time of the New Drug Application submission, three publications or study reports cited in the Clinical section (Section 8) had not been received. Copies of these recently received documents are enclosed; they are listed below with reference to their intended location in the NDA. Attempts to retrieve the remaining two outstanding articles have been unsuccessful (Lampe L., 1979 and Speroff L., 1992).

Kubba A.A. and Guillebaud J. 1983. Case of ectopic pregnancy after postcoital contraception with ethinyloestradiol-levonorgestrel. *Br. Med. J* 287: 1343-1344 (Volume 1.20, pg. 08 2694)

Vero T. and Seregley G. 1981. Postcoital contraception with 0.75 d-norgestrel (postinor). *Therapia Hungarica: Hungarian Medical Journal* 29 (1): 31-34 (Volume 1.22, pg. 08 3350)

WHO/ARP. Forthcoming. Working Title: Breastfeeding and lactational amenorrhea: report of multicentre study. Submitted to Fertility and Sterility. (Volume 1.22, pg. 08 3450)

0241

50 Kirkland Way . Suite 204 . Kirkland, WA 98033 . Tel. 425-739-2006 . Fax 425-739-2036 . Internet: seattle@thewcc.com

Dr. Rarick, M.D.
27 April 1999
Page 2

In addition, one publication was inadvertently omitted in Section 6. A copy of the citation identified below is also attached.

Hümpel M., Wendi H., Pommerenke G., Weib C., and Speck U. 1978.
Investigations of pharmacokinetics of levonorgestrel to specific consideration of possible first-pass effect in women. *Contraception*. 17:207-220
(Volume 1.10, pg. 06 1077)

If you have any questions, please do not hesitate to contact us.

Very cordially yours,

Sharon Camp

Sharon L Camp, Ph. D.
President

WOMEN'S
CAPITAL
CORPORATION

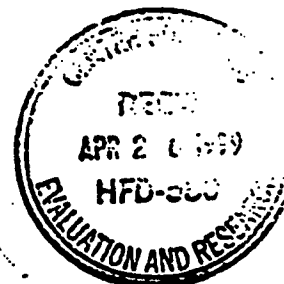
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ORIGINAL AMENDMENT

AM

26 April 1999

Lisa Rarick, M.D.
Division Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857



Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Serial No. 005
Response to FDA Request (Clinical)

Dear Dr. Karick:

Please refer to WHO/HRP 1998 - Study 92908, the pivotal clinical study included in NDA 21-045. In response to a request made by Christina Kish on 14 April 1999, please find enclosed a by-subject listing describing follow-up menses. The follow-up menses have been categorized as requested by the medical reviewer: by duration, by relative amount of bleeding, and by expected onset. The data are also provided electronically (archival copy only).

Please do not hesitate to contact me in the event of further questions.

Very cordially yours,

Sharon

Sharon L. Camp, Ph.D.
President

5/4/99 - data sent as requested - Sharon Medical Officer

Kirkland Way, Suite 204, Kirkland, WA 98033, Tel. 425-739-2006, Fax 425-739-2036, Internet: seattle@thewcc.com

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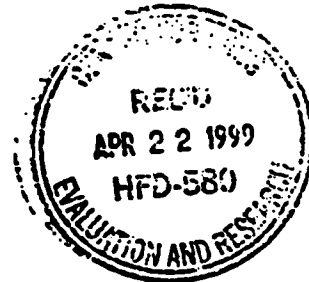
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NEW CORRESP

NC

22 April 1999

Lisa Rarick, M.D.
Division Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857



Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
Correspondence
Serial No. 004

Dear Dr. Rarick:

Women's Capital Corporation (WC) recently requested a meeting with the Division (Serial No. 002, dated 29 March 1999), and that meeting has now been scheduled for 26 April 1999 at 10:30. This letter is to update you on the list of meeting participants.

In addition to myself, Dr. Gordon Duncan of WCC, Dr. Karin Kook of Salamandra, LLC (a regulatory consultant to WCC), and Michael Anisfeld (a GMP consultant to Gedeon Richter) will also be attending the meeting. Dr. Andras Pap will not be able to attend.

We look forward to a productive meeting on 26 April 1999.

Very cordially yours,

Sharon L. Camp

Sharon L. Camp, Ph.D.
President

REVIEWS COMPLETED		
CSO ACTION:		
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.	<input type="checkbox"/> MEMO
CSO INITIALS	DATE	

WOMEN'S
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BC



Reviewed
See Chem. Rev #1
dated 5/12/99
DTC
5/13/99

12 April 1999

Lisa Rarick, M.D., Division Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-045
Levonorgestrel Tablets
as Emergency Contraception
CMC Amendment
Serial No. 003

Dear Dr. Rarick:

Women's Capital Corporation (WCC) recently requested a meeting with the Division, and that meeting has now been scheduled for 26 April 1999 at 10:30 (Serial No. 002, dated 29 March 1999). Since the time of the request, WCC has been informed that the current manufacturing facility, Chemical Works of _____ will be inspected on 17 to 20 May.

The primary purpose of the upcoming meeting with the Division and the chemistry, manufacturing, and controls reviewer is to discuss: (1) the likely expiration dating period for the proposed product in light of the stability data now available and expected during the review cycle; (2) the planned renovations and plant relocations at _____ and their impact on the production of commercial supplies over the coming year; and (3) WCC's request for a variance relative to the proposed commercial label.

Dr. Andras Pap, Manager, Formulation Manufacturing, _____ will be attending the meeting in order to answer any questions regarding the renovation and relocations. In addition to myself, Dr. Gordon Duncan of WCC and Dr. Karin Kook of Salamandra, LLC (who is a regulatory consultant to WCC), will also be attending the meeting.

As promised, additional CMC information is being provided in preparation for the meeting. The information contained in this submission is organized into four attachments. Specific topics for discussion are provided in Attachment 1. Attachment 2 contains an overview of the stability data currently available and _____ most recent stability report. The report includes additional stability data for nine lots of the proposed commercial drug product packaged in two-tablet blister packs. WCC's understanding of the extent of the changes envisioned for the new formulation and packaging facilities is provided in Attachment 3.

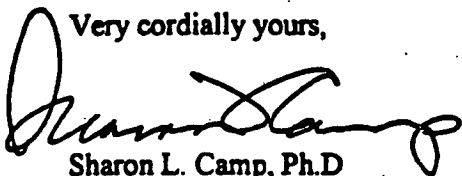
Kirkland Way . Suite 204 . Kirkland, WA 98033 . Tel. 425-739-2006 . Fax 425-739-2036 . Internet: seattle@thewcc.com

Dr. Lisa Rarick
12 April 1999
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Finally, the final report of *in vitro* dissolution experiments requested by the FDA is included in Attachment 4. Although the dissolution method has been demonstrated to be discriminating, a series of experiments were conducted evaluating the various testing parameters. A desk copy of this report will be provided to Dr. Angelica Dorantes of the Division of Pharmaceutical Sciences in conjunction with a separate submission.

Thank you in advance for meeting with us to discuss these CMC topics and issues. We look forward to a productive meeting on 26 April 1999.

Very cordially yours,



Sharon L. Camp, Ph.D
President

Enclosures

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

**WOMEN'S
CAPITAL
CORPORATION**



March 29, 1999

Lisa Rarick, M.D., Division Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-045
Levonorgestrel Tablets as Emergency Contraception:
Request for CMC Meeting
Serial No. 002

Dear Dr. Rarick:

Please refer to the recently submitted New Drug Application for levonorgestrel 0.75 mg tablets for use as emergency contraception (NDA 21-045 submitted 29 January 1999). As indicated in the cover letter to the NDA, Women's Capital Corporation (WCC) will be providing additional stability data within 90 days of submission of the application. As this important milestone in the review process nears, WCC would like to request a meeting with Division management and the reviewing chemists to discuss several chemistry, manufacturing, and controls (CMC) issues. Specifically, we would like to discuss the stability data and projections for the expiration dating period. In addition, we would like to inform the Division about planned renovations at the that will result in temporary closure of the formulation and packaging plants (from June and May, respectively, until September) and to discuss the implications for inspection and production of commercial supplies.

Given the importance of these issues, we would like to schedule the meeting to occur before 29 April and propose any time during the week of April 19, 1999. We expect to be able to provide a detailed briefing package no later than April 12, 1999. Included in the briefing package will be a list of specific questions and the following information:

- Recent drug product stability data from
- A more detailed discussion of the planned renovations;
- A detailed meeting agenda; and
- A list of WCC participants in the proposed meeting.

Thank you in advance for working with us on the proposed meeting.

Sincerely,

Sharon Camp as

Sharon Camp, Ph.D.
President

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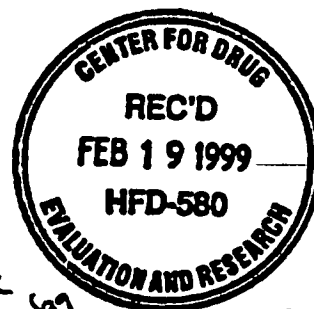
WOMEN'S
CAPITAL
CORPORATION

ORIGINAL

NEW CORRESP

February 11, 1999

Christina Kish, Project Manager
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Parklawn Building, Room 17-B-45
5600 Fishers Lane
Rockville, Maryland 20857



Re: NDA 21-45
Levonorgestrel emergency contraception
Authorized Representatives for WCC

Dear Christina:

The following individuals are authorized to communicate directly with the FDA on behalf of Women's Capital Corporation on the topics indicated:

Gordon W. Duncan, Ph.D., Executive Vice-President WCC (all issues)
Karin Kook, Ph.D, Managing Director, Salamandra, LLC (all IND and NDA issues)
Alan Kaplan, Esq. Kleinfeld, Kaplan & Becker (market exclusivity)
David Adams, Esq. Venable (trade name appeal and labeling)

Please call me if any further clarification is needed.

Cordially yours,

Sharon L. Camp, Ph.D.
President & CEO

NAP-OK-2/22-DDanni

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

land Way . Suite 204 . Kirkland, WA 98033 . Tel. 425-739-2006 . Fax 425-739-2036 . Internet: seattle@thewcc.com

WOMEN'S
CAPITAL
CORPORATION



DUPLICATE

NC

3 February 1999

Lisa Rarick, M.D.
Division Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857



Re: NDA 21-045
Levonorgestrel Tablets
Information Amendment:
Audit of 21 Clinical Centers
Serial No. 001

Dear Dr. Rarick:

On 29 January 1999, Women's Capital Corporation (WCC) submitted a New Drug Application (NDA) for levonorgestrel for emergency contraception. Family Health International has communicated with all 21 centers participating in the Pivotal Study 92908 to determine their auditability and to provide the specific information on each center requested by the FDA. A report of the findings is enclosed. As agreed during a pre-NDA meeting on clinical issues held 23 April 1998, the Division will inform WCC as soon as practicable about the sites chosen for audit so that the necessary preparations can be undertaken.

Please do not hesitate to contact me with any questions.

Very cordially yours,

Sharon L. Camp, Ph.D.
President & CEO

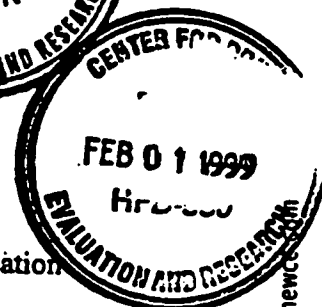
**WOMEN'S
CAPITAL
CORPORATION**



January 29, 1999

Lisa Rarick, M.D.
Division Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Parklawn Building, Room 17-B45
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-045
Levonorgestrel Tablets
As Emergency Contraception
Submission of New Drug Application
Volumes 1.1 to 1.38



Dear Dr. Rarick:

This New Drug Application (NDA) is submitted by Women's Capital Corporation (WCC) in response to the FDA's call, in February of 1997, for applications from industry for new dedicated products for use in emergency contraception. Because the WCC product is highly effective and better tolerated than the Yuzpe regimen currently available to American women, we request that the FDA grant this application priority review.

The clinical data presented in this NDA reflect agreements reached with the FDA's Division of Reproductive and Urologic Drug Products at pre-NDA discussions in March 1997 and April 1998. The NDA contains data from two well-controlled randomized clinical studies on levonorgestrel for emergency contraception: 1) the Pivotal Study of 1,998 women conducted in 21 study centers in 14 countries on five continents by the Special Programme of Research, Development and Research Training in Human Reproduction (WHO/HRP); and 2) a smaller precursor study of 840 women sponsored by WHO/HRP in Hong Kong.

Under contract with WCC, Family Health International (FHI) has performed supplementary statistical analysis of the primary endpoints and prepared the final clinical report on the Pivotal Study. FHI and WCC have also prepared a report characterizing the 21 study centers. The report, which is being submitted under separate cover, indicates that all centers would be prepared to undergo an FDA audit and that all data and correspondence related to the study have been retained. However, advance preparations will be needed in five foreign centers to ensure FDA access to confidential client records.

WCC has purchased from WHO/HRP exclusive rights to access and use the data contained in the Pivotal Study and, therefore, believes it is entitled to a grant of three years of non-patent exclusivity under the provisions of 21 CFR Section 314.108.

01 0003

January 29, 1999

Dr. Lisa Rarick

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The two controlled studies indicate that the levonorgestrel regimen is significantly more effective than the Yuzpe regimen already approved by the FDA. In the Perfect Use Population, the levonorgestrel regimen prevented 89% of expected pregnancies, compared to 74% in the Yuzpe group. Even among women who initiated treatment 49 hours or more after unprotected sex, the levonorgestrel regimen prevented over 60% of expected pregnancies, compared to 40% in the Yuzpe group.

In the Pivotal Study, differences between the levonorgestrel and Yuzpe groups in side effects were highly significant. In the April 1998 meeting with the Division, it was agreed that the endpoints of the WCC safety analysis would be nausea and vomiting. In the levonorgestrel group, 23.1% of Pivotal Study subjects reported nausea and 5.6% vomited, compared to 50.5% and 18.8%, respectively, of the subjects in the Yuzpe group. Nausea is thus reduced by more than 50% and vomiting by 70%.

In addition to the two well-controlled clinical studies, the NDA also contains supporting data from three multicenter clinical studies, sponsored by WHO/HRP, of single doses of levonorgestrel 0.75 mg tablets and 32 additional single-center clinical studies of oral levonorgestrel in various doses. Together with the two well-controlled studies, these supporting studies bring to over 15,700 the total number of women for whom clinical data on postcoital levonorgestrel use are summarized in the NDA. There were no serious adverse reactions reported in the Pivotal Study or in other clinical studies. Reported side effects were generally mild-to-moderate and of short duration. Also included in the NDA are findings from the WCC-sponsored two-period crossover pharmacokinetic study requested by the FDA and a summary of other studies from the literature. All relevant literature on pre-clinical studies is reviewed.

The proposed commercial product is composed of two levonorgestrel 0.75 mg tablets manufactured and put into blister packages by

maintains a current Drug Master File at the FDA for the levonorgestrel drug substance used in the tablets. The same tablet, with minor formulation changes, was used in the Pivotal Study and most other clinical studies summarized in the NDA. Postinor brand levonorgestrel tablets have been manufactured by since 1980, and are currently approved for occasional postcoital contraception in 34 countries, including all of Eastern Europe and the former Soviet Union. Postinor is marketed in four-count and ten-count blister packages. National and international pharmacovigilance agencies were queried for reports of adverse reaction to Postinor. Only one adverse reaction was reported involving a Hungarian woman who took five levonorgestrel 0.75 mg tablets at one time.

Long-term and accelerated stability data on the tablet are presented in this NDA. Data on tablets manufactured between 1992 and 1997 and stored in bulk or packaged in four-count or ten-count blisters are satisfactory for as long as 60 months at 25°C/60% relative humidity (RH) and for as long as 9 months under accelerated conditions of 40°C/75% RH. Subsequent to a September 1997 plant renovation involving minor changes in equipment, some problems have been observed in dissolution test results. This deviation from release specifications is under investigation, and is committed to resolving the issue

January 29, 1999

Dr. Lisa Rarick

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specifications is under investigation, and is committed to resolving the issue quickly and generating additional stability data necessary for FDA approval. Additional data from 16 ongoing stability studies on eight batches of drug product recently and packaged by in two-count and four-count blisters, will be available within 90 days of the date of submission.

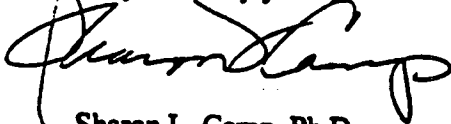
The drug product will be tested and released by prior to shipment and again by prior to secondary packaging by

Proposed labeling reflects the trade name, PLAN B, originally proposed to the FDA. WCC presently intends to appeal the decision of the CDER Labeling and Nomenclature Committee that the trade name is unacceptable. If the appeal is not successful, WCC will immediately propose a new trade name.

Because of the demonstrated superiority of the new levonorgestrel regimen and the excellent safety profile of the levonorgestrel tablets manufactured by for nearly two decades, the proposed WCC product for emergency contraception should be approved for sale on a priority basis, so the improved regimen may replace the older Yuzpe regimen of high-dose oral contraceptives in all family planning formularies. Although the same levonorgestrel regimen may be created with a total dose of 40 progestin-only oral contraceptives, this cumbersome and expensive option will not be accessible to most American women.

We thank you and your colleagues for your patience and assistance through our lengthy pre-NDA discussions and look forward to assisting you in an expedited review of this NDA.

Very sincerely yours,



Sharon L. Camp, Ph.D.
President

01 0005